Remarks

Prior to entry of this amendment, claims 1-42 were pending in the application. Claims 8-9 and 31-32 are canceled herein. Applicants expressly reserve the right to pursue protection of any or all of the canceled subject matter in one or more continuing applications. Claims 1, 20 and 23 are amended herein. Claim 1 is amended to incorporate the limitations of claim 9. Claim 23 is amended herein to incorporate the limitations of claim 32. Support for the amendment of claim s 1 and 23 may be found throughout the specification. Support for the amendment of claim 20 can be found throughout the specification, such as on page 31, lines 16-21; page 32, lines 25-30; and page 34, line 18 to page 35, line 14.

New claims 43-47 are added herein. Support for new claims 43-47 can be found throughout the specification, such as on page 29, line 1 to page 32, line 5; page 21, lines 11-21, original claims 1, 3, 5 and 17; and page 35, lines 15-26, and in the original claims.

The specification is amended herein to properly refer to trademarks and correct typographical errors. Example 3 of the specification is amended herein to correct the reference to the figures, as supported in the specification on page 5, lines 11-30, Figs. 6-8, and page 35, line 15-26.

No new matter is introduced by the foregoing amendments or the new claim. After entry of this amendment, **claims 1-7, 10-30, and 33-47 are pending in this application**. Reconsideration of the pending claims is requested.

Restriction Requirement

The election with traverse of the species of a) acute respiratory distress syndrome, b) inhalation, c) anti-inflammatory agent, and d) SEQ ID NO: 1 for initial prosecution was acknowledged in the Office action. Applicants expressly reserve the right to petition the restriction requirement.

Priority

Applicants thank the Examiner for acknowledging the priority claim.

Specification

The specification is amended herein to include trademarks in all capital letters. The specification is also amended herein to correct the reference to the figures, as supported on page 5, lines 11-30, Figs. 6-8, and page 35, line 15-26.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-41 were rejected under 35 U.S.C. § 112, first paragraph as allegedly the specification is not enabling for methods of treating a subject who is at risk for developing an inflammatory lung disease. Applicants respectfully disagree with this assertion.

The Office action alleges that the specification is only enabling for a method of treating inflammatory lung disease in a subject *using cells* that includes administering a therapeutically effective amount of a suppressive oligodeoxynucleotide (ODN). However, the Office action alleges that the specification is not enabling for (1) the claimed ODNs or (2) an *in vivo* method of treating inflammatory lung disease using a therapeutically effective amount of a suppressive ODN or. Applicants respectfully disagree with these assertions.

Applicants submit that one of skill in the art could readily make and use the claimed ODNs without undue experimentation. A Wands analysis is provided below:

(A) Breadth of the claims: The claims are limited to the treatment of an inflammatory lung disease using a suppressive ODN that is at least about 8 nucleotides in length, forms a G-tetrad, has a CD value of greater than about 2.9, and comprises at least two guanosines, wherein the oligodeoxynucleotide is from about 10 to about 30 nucleotides in length. Claims 17 and 41 recite specific nucleic acid sequences of use in the claimed methods.

(B) The nature of the invention: The claims are directed to methods of treatment that utilize nucleic acid sequences.

(C) The state of the prior art: The synthesis of ODNs is well known in the art, as is the administration of ODNs to a subject of interest. There are art-recognized models for testing therapies for the treatment of inflammatory lung disease.

(D) The level of ordinary skill in the art: The level of skill of a molecular biologist and/or pulmonologist is high.

(E) The level of predictability in the art: The production of ODNs with specified characteristics is routine. There are art recognized models for inflammatory lung disease (such as the one described in the examples section) that can be used to confirm the effect of an ODN of interest. The administration of agents to a subject for the treatment of inflammatory lung disease is described (see the specification, page 24, line 9 to page 30, line 10); the pharmaceutical formulations and methods of administration are routine to one of skill in the art.

(F) The amount of direction provided in the specification: The specification discloses the physical characteristics of ODNs of use, namely that they (1) are 10-30 nucleotides in length, (2) have a CD value of greater than about 2.9 (for example, see the specification on page 20, lines 15-24), and (3) form a G-tetrad (for example, see the specification on page 20, lines 7-14). General classes of ODNs that have these characteristics are provided (see the specification on page 21, lines 1-10), and at least 25 examples of suppressive ODNs are provided (see the specification on page 21, lines 11-21, and SEQ ID NOs: 1-25). In addition, pharmaceutical compositions and methods of administration of ODNs are described in the specification (see page 24, line 9 to page 30, line 10). Methods for confirming the effectiveness of an ODN, such as by monitoring lung function are disclosed (see the specification at page 30, line 11 to page 31, line 15).

(G) The existence of working examples: Numerous exemplary ODNs of use are described in the specification (see, for example, page 21, lines 15-21 and SEQ ID NOs: 1-25). The effectiveness of these ODNs in inhibiting an immune response *in vitro* is disclosed (see Example 2). The use of an exemplary ODN (SEQ ID NO: 1) in an animal model of inflammation is described in the specification (see Example 3). Thus, a working example is provided.

(H) The quantity of experimentation required: There is substantial guidance provided on the synthesis of ODNs and formulation of ODNs for delivery to a subject (see, for example, page 19, line 26 to page 24, line 7). The synthesis of ODNs is automated and routine. Thus, only limited experimentation is required to practice the claimed invention.

With regard to the use of suppressive ODNs, Applicants submit that the specification is fully enabling for methods for treating inflammatory lung disease, wherein the methods include the administration of a therapeutically effective amount of a suppressive ODN *in vivo*. The Office action states that the specification describes only general methods. The Office action further describes that Example 2 describes the use of suppressive ODNs to inhibit the secretion of cytokines from RAW 267.4 macrophage cells *in vitro*. Applicants agree that *in vitro* data is presented in Example 2, documenting the effect of suppressive ODNs on macrophage cells (which are important in the etiology of inflammatory lung disease).

However, additional data is presented in the specification. Example 3 demonstrates that suppressive ODNs block CpG-induced inflammation in an animal model, namely a mouse model of inflammatory lung disease. The Office action alleges that Example 3 utilizes RAW 267.4 cells, which is not correct. Page 33 of the specification describes the animal procedures:

> "Eight to twelve week old BALB/c mice (Jackson Laboratories, Bar Harbor, Maine) were maintained in an SPF facility. Animals were anesthetized with inhaled isoflurane, *and ODNs administered intratracheally using a sterile, blunt, fine bore needle.* At various times post treatment, animals were sacrificed. The trachea was exposed by a midline incision, an 18-gauge catheter inserted, and the lungs lavaged 4 times with 1 ml aliquots of PBS. The BAL fluid was pooled, centrifuged at 500 x g for 10 minutes at 4°C. Supernatants were stored at -70°C until assay. Cell pellets were resuspended in PBS, counted, spun onto a glass slide (Cytospin 2; Shandon, Pittsburg, PA), and individual cell types quantitated following staining with Diff-Quik (Dade Behring Inc., Newark, DE)." [emphasis added]

It is clear from this description that the ODNs are suspended in a carrier and administered to the animal intratracheally. Macrophage cells, such as RAW 267.4 cells, are **not** used at any time in this animal model.

The specification describes results obtained in this animal model in Example 3, page 35, line 15 to page 36, line 3 and Figs. 6-8. Specifically, it is disclosed that immunostimulatory CpG DNA instilled into the lungs of mice triggers inflammation. The administration of an exemplary inhibitory ODN, namely an ODN with a nucleic acid sequence set forth as SEQ ID NO: 1 (see the methods section page 32, line 17) resulted in a reduction in inflammation, as measured by the production of inflammatory cytokines and neutrophil infiltration (see page 35, lines 21-26 and Fig. 4). It is clear from the results presented in the specification that direct administration of a suppressive ODN, such as an ODN having the nucleotide sequence set forth as SEQ ID NO: 1, can be used to treat inflammatory lung disease.

The Office action cites several references, such as Goldberg et al. (Immunol. Lett. 73: 13-18, 2000, copy not provided to the Applicant). Goldberg et al. describes immunostimulatory CpG ODN and their role in disease. The Office action indicates that Goldberg et al. state that ODNs merit further study. Applicants do not deny that in 2000 Goldberg suggested that immunostimulatory ODNs should be studied to determine their role in disease. However, the present application describes the use of immunosuppressive ODNs, NOT immunostimulatory ODNs. Thus, the ODNs described in the present application are *completely different* than the ODNs discussed in Goldberg et al. Moreover, the statements made in Goldberg et al. (albeit in 2000, two years before the priority date of the present application), suggest that *ODNs could be of use.* It is the work of the Applicants that defines both the sequence of the specific ODNs of use (namely that they are not unmethylated CpG ODNs but are of 10-30 nucleotides in length with a defined CD value and form a G-tetrad) and the utility (in treating inflammatory lung disease) of the claimed ODNs.

The Office action further refers to Heeg et al., International Archives of Allergy and Immunology, page 93, 2000. Heeg et al. states that immunostimulatory CpG ODNs have been used as vaccine adjuvants and selectively induce a Th1 response, and suggest that these ODNs could be used for the treatment of allergy. The Office action alleges that Heeg et al. question whether experiments performed in mice will be successful in humans. However, the quotation cited in the Office action states "the data so far indicate that human cells respond in a similar way to murine cells." Thus, although Heeg et al. describe the effects of completely different ODNs (those that are immunostimulatory), it appears that Heeg et al. conclude that human cells will respond to ODNs in a manner similar to murine cells, and suggests that ODNs could be used in immunotherapy (see the last sentence of the abstract). Applicants submit that, contrary to the negative statements made in the Office action, Heeg et al. supports the assertion that a description that sets forth specific ODN sequences, and provides data in an animal model that these ODNs are effective, provides enablement for the treatment of humans.

Broide et al. (J. Immunol. 161: 7054-7062, 1998) describes that the mouse model of allergen induced hyperresponsiveness to demonstrate that an immunostimulatory ODN with a CpG motif (again, not the inhibitory ODNs of the present application) can be used to inhibit airway eosinophila and reduce responsiveness to the triggering agent. Briode et al. state (page 7062) "In summary, ISS-ODN [immunostimulatory ODN] administration provides an alternative to the current practice of allergen protein desensitization, which has relative low efficacy and high potential for side effects, such as anaphylaxis..." The Office action cites this reference as demonstrating that there are limitations on anti-inflammatory agents for the treatment of inflammatory lung disease. However, Broide et al. are commenting on the limitations of allergen protein desensitization, NOT on the limitations of ODN therapy. Any negative statements made by Broide et al. four years prior to the priority date of the present application with regard to other treatments such as allergen protein desensitization, and the suggestion that ODNs should be further studied, simply cannot negatively reflect on the present disclosure. The Applicants clearly have demonstrated that the immunosuppressive ODNs can be used to treat inflammatory lung disease, and have described these methods in sufficient detail for one of skill in the art to make and use the claimed invention.

The Office action further refers to Bernard et al. (Amer. J. Resp. Crit. Care Med. 72: 798-806, 2005) as describing that corticosteroids are a standard therapy for inflammatory lung disease. The Office action appears to allege that this post-filing date reference suggests that treatment for ARDS simply is not possible. However, this is in stark contrast to the conclusions of Bernard et al., who begin by stating "....the advances made even in the past 50 years are staggering when compared with all else that came before..." (see page 798). Bernard et al. do describe the use of corticosteroids as controversial (see page 803). However, Bernard et al. suggest that there is considerable promising work, such as from the NHLBI using modern techniques such as microarrays and proteomics. Indeed, Bernard et al. summarizes how effective new techniques could be on page 804:

> "The past 100 years (especially the last 50 years) of ARDS research and advances in the clinical care of patients with ARDS is a fascinating picture that spans the timeframe of so many other major medical and scientific advances. Tools such as the highly instrumented animal model, cell biology, molecular biology, advances in imaging from the micro to macroscopic, and genetics have greatly facilitated

> our understanding of this complex syndrome. The scientific foundation is strong and will provide a firm basis upon which the next chapter in this saga can be written. With only a little imagination, a day can be seen when the mortality and the long term morbidity of ARDS will be reduced to only that of the preexisting underlying diseases, if any."

Thus, Bernard et al. simply cannot be viewed as providing evidence that inflammatory lung disease cannot be treated by any method. Contrary to the negative assertions in the Office action, Bernard et al. actually suggest that new strategies for the treatment of inflammatory lung disease could be very effective. Thus, Bernard et al. does not negate the results presented in the specification.

The Office action states that the "murine model is generally the experimental animal used in studies for inflammatory lung disease or lung injury. Animal models of lung injury have been useful in the mechanisms in inflammatory lung disease. However, using an animal model that mimics key aspects of human inflammatory lung disease has been limited." In support of this statement, the Office action cites Matthay et al., (American J. Resp. Crit. Care Med 167: 1027-1035, 2003). This article describes the recommended future research directions for acute lung injury suggested by the NHLBI working group. This article states (page 1032) "Animal studies that have attempted to mimic human ALI/ARDS have been useful and will likely continue to provide valuable observations regarding both the mechanisms underlying the pathogenesis, progression and resolution of this syndrome and ways in which its course can be modulated therapeutically." Although Matthay et al. discloses that the there is uncertainty about which of the many available animal models most accurately reflects the human clinical syndrome, this article suggests that the study of animal models can be used to evaluate "the effect of agents having the potential to diminish the severity of systemic and pulmonary injury…" (see the sentence bridging pages 1032-3). Thus, contrary to the negative conclusions asserted in the Office action, Matthay et al. also support the conclusion that treatments can be demonstrated to be of use in animal models (such as the one described in the examples section of the present application.

The Office action further cites van der Vliet (Resp. Res. 1: 67-72, 2000) as describing shortcomings of several animal models of respiratory tract disease. Applicants do not deny that every animal model does not replicate every aspect of a human disease process. However, this does not negate the overall utility of animal studies. Submitted herewith as Exhibit A is Dawkins and Stockley ("Animal models of chronic obstructive pulmonary disease," Thorax 56: 972-977, 2001), which describes the usefulness of animal models of respiratory disease. For example (see page 972, first column):

> Animal models act as a bridge between in vitro studies in the laboratory and studies of humans. As such, they have had a major impact on the investigation of many medical conditions...animal models can provide a framework for the rational and safe design of expensive and long term clinical studies.

This article concludes (page 976):

> Rodents and humans have certain anatomical and physiological differences in the broncopulmonary trees but mount similar host responses to lung challenge....Such approaches will not only increase our understanding about pathogenesis, but will also facilitate the development and introduction of new therapeutic strategies.

Animal models are known to be of use for studying acute lung injury. For example, Metz and Sibbald (Chest 100: 1110-9, 1991, copy submitted as Exhibit B) states:

> A wide variety of animal models have been developed to explore both the pulmonary and nonpulmonary sequelae of acute lung injury. Common to a majority of these models has been the description of a diffuse inflammatory reaction in the lung's microvasculature....recent data from animal studies of anti-inflammatory therapy in ALI have generated interest in clinical trials of anti-inflammatory therapy for ARDS.

Thus, one of skill in the art is not "accepting on its face that the examples given in the specification as being correlative or representative of the successful treatment or inhibition of inflammatory lung disease in any subject (human or otherwise)" (see the Office action, page 11). Rather, one of skill in the art would evaluate the data presented in an **art-accepted** animal model of inflammatory lung disease, and agree that the Applicants have clearly enabled the treatment of inflammatory lung disease (as the data presented document that the claimed ODNs are efficacious).

The MPEP § 2107.03 states:

> As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v.*

> *Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980).... If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process.... Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974))."

In the present application, the *in vitro* and *in vivo* results both document the activity of the claimed ODNs for the treatment of inflammatory lung disease. MPEP § 2164.02 states:

> An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention....In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.

Working examples are provided both in vitro (RAW 264.7 cells, Example 2) and in vivo (mouse model of lung inflammation, Example 3). The MPEP clearly states that results from an art-accepted an model (and *in vitro* data) should be accepted as a showing that the claimed invention is enabled. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 1 is rejected under 35 U.S.C. § 112, first paragraph as allegedly not complying with the written description requirement. The Office action alleges that there is insufficient written description is provided for an ODN of "at least about 8 nucleotide in length" that "forms a G tetrad" and "has at least two guanosines." Applicants respectfully disagree with this rejection. Applicants note only claim 1 was included in the rejection. Thus, it is the Applicants understanding that the U.S. PTO considers there to be sufficient written description for the remaining claims. Solely to advance prosecution, claim 1 is amended herein to incorporate the limitations of claim 9, and thus to be limited to nucleotides of 10 to 30 nucleotides in length. Applicants submit that this amendment overcomes the rejection.

With regard to written description: The specification discloses the physical characteristics of ODNs of use, namely that they (1) are 10-30 nucleotides in length, (2) have a CD value of greater than about 2.9 (for example, see the specification on page 20, lines15-24), and (3) form a G-tetrad (for example, see the specification on page 20, lines 7-14). General classes of ODNs that have these characteristics are provided (see the specification on page 21, lines 1-10), and at least 25 examples of suppressive ODNs are provided (see the specification on page 21, lines 11-21, and SEQ ID NOs: 1-25). In addition, pharmaceutical compositions and methods of administration of ODNs are described in the specification (see page 24, line 9 to page 30, line 10). Methods for confirming the effectiveness of an ODN, such as by monitoring lung function are disclosed (see the specification at page 30, line 11 to page 31, line 15).

The Office action (see page 14) cites the Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, paragraph 1 as stating "possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show the invention was complete, by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." Applicants would like to draw the Examiner's attention to a drawing (Figure 1A), which illustrates the specific structure of an oligodeoxynucleotide that forms a G tetrad. As described in the specification, a G tetrad involves the planar association of guanosines in a cyclic Hoogsteen hydrogen bond arrangement. The specification provides information on specific physical and stereochemical properties of these structures (see, for example, page 20). G-tertrads can be classified based on the circular dichromotism (CD) values. Specific lengths of ODNs of use are provided. In addition, a specific subclass of ODNs of use is described: ODNs with TTAGGG repeats. Moreover, 25 specific examples of ODNs of use are provided as SEQ ID NOs: 1-25 (see page 21).

An applicant seeking to claim a genus of compounds, such as a nucleic acid must provide a "representative" number of species within the genus. It is well established that an Applicant need not disclose every species encompassed by a claim (In re *Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). In the present application, ODNs with specific physical and stereochemical properties are disclosed. The structure of these molecules is clearly set forth. In addition, 25 examples are provided. Thus, there clearly is sufficient written description for the claimed ODNs.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 20 was rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for not reciting either in vitro or in vivo. Claim 20 is amended herein to indicate that the cell is in vitro, thereby rendering the rejection moot.

Information Disclosure Statements: Claims Free of the Prior Art of record

Two Information Disclosure Statements were submitted for the present application, one dated October 7, 2003, and one dated March 31, 2005. For the Examiner's convenience, copies of the PTO-1449 forms are included with this response. Applicants respectfully request that the Examiner initial and date the PTO-1449 to indicate that the cited prior art has been considered.

The Office action has cited U.S. Patent No. 6,214,806 (hereinafter the '806 patent) as being pertinent, but has not asserted any rejections based on the '806 patent. Thus, it is the Applicants understanding that all of the pending claims were free of the prior art.

Request for a PTO-892

Applicants respectfully request a PTO-892 form be provided to make the references cited in the Office action formally of record in the present application.

SEQ ID NO: 1

Applicants elected the species of SEQ ID NO: 1 for initial prosecution. No rejections based on any prior art were asserted in the Office action. Thus, it is the Applicants understanding that an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 1 is free of the prior art of record.

Data is presented in the specification (see Examples 2 and 3) documenting the effectiveness of an oligodeoxynucleotide comprising the nucleic acid sequence set forth as SEQ ID NO: 1 when used in models (in vivo and in vitro) of inflammatory lung disease. Data is also presented documenting the effect of oligodeoxynucleotides comprising the nucleic acid sequence set forth as SEQ ID NO: 1 on cytokine production (see the examples). Thus, it is clear that the specification is enabling for methods of treating inflammatory lung disease and reducing cytokine production in a subject that include administering to a subject a therapeutically effective amount of an oligodeoxynucleotide comprising the nucleotide sequence set forth as SEQ ID NO: 1. Allowance of new claims 43-47 is respectfully requested.

Request for Interview

If an additional rejection is asserted, or if the present rejections are maintained, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Conclusion

It is respectfully submitted that the present claims are in a condition for allowance. Should the Examiner have further questions or comments with respect to examination of this case, it is respectfully requested that the Examiner telephone the undersigned so that further examination of this application can be expedited.

Respectfully submitted,

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